Remarks

Claims 9, 11, 12 and 14-16 are pending. No new matter is added herein.

Objection to Claim 11

Claim 11 is objected to for being drawn to non-elected subject matter. Applicants note that the Office action dated October 3, 2002 states that "the species not elected from clams 3, 11, and 18 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to a non-elected species." It is the Applicants' understanding that the subject matter of diabetic ischemic neuropathy, and diabetic ischemic myocardial infarction are considered to be withdrawn from claim 11. Claims 3 and 18 are canceled.

The species not elected in claim 11 were withdrawn from further consideration as the generic claim (claim 9) was not considered to be allowable at the time the restriction requirement was asserted (see the Office action dated October 3, 2002). However, following an indication of the allowability of a generic claim (claim 9) to the treatment of diabetic ischemic disease, Applicants submit that the withdrawn species should be rejoined.

Rejections Under 35 U.S.C. §102

Claims 9, 11, 12, and 14-16 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,248,722 (hereinafter the '722 patent). Applicants respectfully disagree with this rejection.

The '722 patent corresponds to published PCT Application No. WO 97/07824, which was published on June 3, 1997. WO 97/07824 is cumulative with the '722 patent. For the Examiner's convenience, WO 97/07824 is listed on the Information Disclosure Statement that accompanies this response.

The '722 patent teaches nucleic acid therapy for treating a subject in which hepatocyte growth factor (HGF) is effective. However, the '722 patent does not suggest that hepatocye growth factor would be effective in the treatment of diabetic ischemic disease. Indeed, the '722 patent discloses that HGF can be used to treat *arterial* diseases. In contrast, diabetic ischemia is a more complex disorder that involves disruptions in the microvasculature (such as the capillaries) as well as the larger blood vessels (such as the arteries).

For the USPTO to find an invention not novel under 35 U.S.C. §102[1] ("anticipated"), a single prior art reference must disclose every element of the invention, either explicitly or inherently.[2] To anticipate, the reference must also enable one of skill in the art to make and use the claimed invention.[3] As the '722 patent does not disclose the treatment of diabetic ischemic disease, it cannot anticipate claims 9, 11, 12, or 14-16.

Moreover, it is known that angiogenesis seldom occurs in a variety of diabetic ischemic diseases. Furthermore, the prognosis is unfavorable in ischemic disease complicated with or caused by diabetes (see the specification at page 2, lines 23-26). The prognosis of occlusive arterial disease in considerably worse in diabetics that in non-diabetics as described in Melliere et al., *Eur. J. Vasc. Endovasc. Surg.* 17: 438-441, 1999 (see the first sentence of the introduction, attached as Exhibit A). Melliere discloses that conventional surgery such as infrainguinal arterial revascularization and percutaneous transluminal angioplasty (PTA) were less effective in diabetics than non-diabetics (see pages 439-440). Indeed the treatments for non-diabetics are not always effective for diabetics; diabetic ischemic disease is clearly different from non-diabetic ischemic disease. In view of the failure of other anti-ischemic therapies, it was not known, nor would it be obvious, to administer HGF to a patient with diabetic ischemic disease.

The Applicants of the above-referenced application determined that HGF therapy is effective for diabetic ischemic diseases. The Applicants also determined that administration of HGF relieves pain from conventional surgery performed on patients with a diabetic ischemic disease. Furthermore, the Applicants determined that the decreased angiogenesis that occurs in diabetic patients is specifically due to a decrease in endogenous HGF expression. The '722 patent does not establish a *prima facie* case of obviousness for the use of HGF therapy in diabetic ischemic disease.

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[1] 35 U.S.C. § 102 states in pertinent part that a person shall be entitled to a patent unless "(b) the invention was patented or described in a printed publication in this or a foreign country . . . . more than one year prior to the date of the application for patent in the United States . . . ."

[2] *See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365, 52 USPQ2d 1303 (Fed. Cir. 1999). The types of prior art that can anticipate an invention are set forth in 35 U.S.C. § 102, and include printed publications that were published more than one year before the filing date of a patent.

[3] *Bristol-Myers* at 1379 citing *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985).

Claims 9, 11, 12 and 15-16 were rejected as allegedly being anticipated by U.S. Patent No. 6,121,246 (Isner et al., herein after the'246 patent). Applicants respectfully disagree with this assertion.

The '246 patent teaches the use of an angiogenic protein, VEGF. Thus, the '246 patent does not anticipate claims 9, 11, 12 and 15-19. Moreover, the '246 patent does not render obvious the use of HGF. As noted in the Office action, the amount of a VEGF-encoding nucleic acid injected is at least 500 μg (see Example 1, claims 6 and 21). The use of higher amounts, such as between 1000 μg and 2000 μg, and between 2000 μg and 4000 μg, are also disclosed (see claims 7, 8, 22 and 23). However, the '146 patent does not teach the use of HGF. In addition, the amount of HGF of use is considerably less than the amount of VEGF of use. Specifically, the use of 50 μg of a nucleic acid encoding HGF is effective, only one tenth the amount of a nucleic acid encoding VEGF. Thus, the use of a nucleic acid encoding HGF provides an unexpectedly superior result.

Rejections under 35 U.S.C. § 103

Claims 9, 11, 12, and 15-16 are rejected as allegedly being obvious over Gene Therapy of Osaka University, English translation from the Japan Financial Newspaper, Local News Section (December 14, 1998).

Submitted herewith is a Declaration Under 37 C.F.R. § 1.132 of Ryuichi Morishita, an inventor of the above-referenced application. Dr. Morishita states that the article in the Japan Financial Newspaper is a report of the inventors' own work. The article describes a request for approval for a clinical trial by the Institutional Review Board (IRB) at Osaka University in Japan. This request was made by Dr. Morishita and Dr. Ogihara. Dr. Morishita decided to proceed with the request for humanitarian reasons, so that patients could benefit from their research immediately (without waiting for a patent application to be filed).

As the article published in the Japan Financial Newspaper is a report of the inventor's own work, published less than one year prior to the filing date of the parent Japanese application, it is clear that the inventors conceived of their invention prior to the publication in the Japan Financial Newspaper. Thus, this newspaper article is not available as a reference. Reconsideration and withdrawal of the rejection is respectfully requested.

The declaration of Dr. Morishita accompanying this response is unsigned. A signed copy of the declaration will be forwarded to the U.S. Patent and Trademark Office as soon as it is received from Japan.

Citation of the Prior Art

The Office action states at page 10 that U.S. Patent No. 5,980,887 is cited on form PTO-892. However, there is a typographical error on the form, which inadvertently lists US. Patent No. 6,908,887. An Information Disclosure Statement is submitted herewith to make PCT Application No. WO97/07824 of record (which is cumulative with US. Patent No. 6,248,722). Thus, for the Examiner's convenience, Applicants have also cited U.S. Patent No. 5,980,887 on the form PTO-1449. Applicants request that the Examiner initial and date the form PTO-1449 to make these two references of record in the present application.

Conclusion

Applicants submit that the claims are in condition for allowance. If any minor matters remain to be addressed before a notice of allowance is issued, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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